REMARKS

Claims 16-22 and 26 remain in the case. Favorable reconsideration is respectfully requested.

The following remarks address the issues presented in the Office Action in the order in which they appear.

Rejection of Claims 16-18, 21-22, and 26 Under 35 U.S.C. §103(a) Over Van Ooyen et al. in View of Virki et al., Henrissat et al., and Willmitzer et al.:

This rejection is respectfully traversed because the overly-broad and generalized teaching of the combined references do not enable, to a reasonable degree of certainty, the transgenic expression of the particular enzymes explicitly recited in the claims.

In making this rejection, the Office states that:

> Applicants have not supplied any rationale why the system disclosed in Van Ooyen et al. would not be useful in the expression of other ***functionally equivalent*** plant polysaccharide-degrading enzymes that are known in the art.... (Emphasis added.)

In response, Applicants ask: functionally equivalent in what manner? "Equivalent" in the sense that the enzymes described in the applied reference catalyze the same reactions as those recited in the present claims? Or "equivalent" in the sense that the enzymes of the prior art can be transformed into a plant host and expressed in the exact same fashion as the presently recited enzymes? In the present case, it would appear that the Office is adopting the second sense of the word "equivalent;" in other words, the Office appears to be taking the position that merely because Van Ooyen **mentions** the transgenic expression of "any enzymes or combination of enzymes which are capable of degrading plant polysaccharides" (col. 4, lines 12-15), the reference necessarily **enables** the expression of all such polysaccharide-degrading enzymes in a plant host. Applicants respectfully submit that this is an overly broad interpretation of the Van Ooyen reference.

More specifically, in the passage spanning col. 4, lines 25-52, Van Ooyen states

that the process described therein is capable of expressing any enzyme selected from the following enzyme classifications (EC):

EC 3.2.1.1, EC 3.2.1.2, EC 3.2.1.3, EC 3.2.1.4, EC 3.2.1.6, EC 3.2.1.7, EC 3.2.1.8, EC 3.2.1.20, EC 3.2.1.21, EC 3.2.1.22, EC 3.2.1.23, EC 3.2.1.24, EC 3.2.1.25, EC 3.2.1.37, EC 3.2.1.39, EC 3.2.1.40, EC 3.2.1.41, EC 3.2.1.51, EC 3.2.1.55, EC 3.2.1.65, EC 3.2.1.68, EC 3.2.1.78, EC 3.2.1.89, EC 3.2.1.90, EC 3.2.1.91, and EC 3.2.1.99.

This generic list of enzymes, recited according to the reactions catalyzed by the enzymes themselves, literally encompasses an enormous number of different enzymes derived from any source, microbial or otherwise.

In contrast, the present Claim 16 explicitly recites exactly four specific enzymes by source organism and name, not by functionality: *T. fusca* cellulase E2, *T. fusca* cellulase E3, *T. reesei* CBH I, and *A. cellulolyticus* endoglucanase E1.

At the heart of this rejection is a dichotomy between "functional" similarity or identity and "structural" similarity or identity. In the field of enzymes, while many enzymes share functional similarities, their structural features can be remarkably different. Van Ooyen et al.'s disclosure, in combination with the other cited references, does not render the present claims *prima facie* obvious because the description in Van Ooyen is directed to functional aspects of enzymes, rather than structural aspects, and are far too general to be of practical import to the instant claims.

"Structural" obviousness, in the chemical sense, is predicated upon the assumption that compounds having similar **structures** will have similar **functions** or properties. Thus, prior art chemical structures that are closely related to a claimed compound, such as homologs, analogs, or isomers, will raise an inference of *prima facie* obviousness, without any further showing on the part of the PTO. See, for example, *In re Dillon*, 16 USPQ2d 1897 (Fed. Cir. 1990, *en banc*), *cert. den'd.*, 111 S.Ct. 1682 (1991). The case law, however, does not support the Office's present reasoning, that enzymes having similar **functions** (but clearly distinct structures) will behave similarly when an attempt is made to transform and express these enzymes in a transgenic plant host.

In this regard, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1990), *cert. den'd.*, 112, S.Ct. 169 (1991), is highly instructive. In that case, the Federal Circuit held that using baboon EPO as a probe, a compound and a use both known in the prior art, did not render obvious the use of baboon EPO as a probe to isolate the human EPO gene, despite the fact that the corresponding baboon and human DNA are approximately 90% identical. In short, while a proper case of *prima facie* obviousness can be made starting **from** a closely-related prior art structure and extending **to** function, a *prima facie* case of obviousness cannot be established in the reverse direction, *i.e.*, starting from function and extending to structure. The lack of motivation in the "function-to-structure" direction is due to a wholly inadequate understanding of the relationship of **function** to **structure** (as contrasted to the established relationship extending from structure to function). See, for example, *Hormone Research Foundation Inc. v. Genentech, Inc.*, 15 USPQ2d 1039, 140-141 (Fed. Cir. 1990), *cert. dismissed*, 111 S.Ct. 1434 (1991).

While the Van Ooyen reference clearly **mentions** an extremely large number of enzymes that could *conceivably* be expressed using the methodology described therein, the reference only adequately describes the expression of two enzymes: the expression of alpha-amylase (from *B. licheniformis*) in transgenic tobacco and tomato, and the tuber-specific expression of both alpha-amylase (*B. licheniformis*) and glucoamylase (from *A. niger*) in potato. See Examples 4, 8, and 12 of Van Ooyen. Alpha-amylase is cataloged functionally as EC 3.2.1.1 (see Van Ooyen, col. 4, lines 25-26) and glucoamylase is cataloged functionally as EC 3.2.1.3 (Van Ooyen, col. 4, lines 26-27, "glucoamylase" is synonymous with "amyloglucosidase"). In contrast, the enzymes recited in the present claims are classified as follows:

T. fusca cellulase E2 = 3.2.1.4

T. fusca cellulase E3 = 3.2.1.91

T. reesei CBH I = 3.2.1.91

A. cellulolyticus endoglucanase E1 = 3.2.1.4

The enzymes recited in the present application are different in both structure and

function to those enzymes whose transgenic expression in a plant host is adequately enabled by the Van Ooyen reference.

Thus, the combined references also fail to provide a reasonable expectation of success at arriving at the presently claimed invention. As noted above, the primary reference to Van Ooyen mentions a wide range of enzymes that conceivably could be produced in a plant host. The reference itself, however, discloses only two enzymes, alpha-amylase from *B. licheniformis*) and glucoamylase from *A. niger*, that were successfully transformed into a plant host. It remains wholly uncertain based upon the detailed description of the Van Ooyen reference whether or not the other enzymes that are simply mentioned in the document can be expressed in a plant host.

The law of obviousness in this regard is straightforward: if one or more references provide technical motivation for arriving at the claimed invention, the combined references must provide a reasonable expectation of success. Such a reasonable expectation is lacking in the present rejection because the combined documents neither provide sufficient direction to arrive at the present invention, nor do they enable the present invention. As noted above, the Van Ooyen reference mentions a great number of enzymes, but enable the transgenic production of only two, alpha-amylase and glucoamylase. These two enzymes are clearly distinct from those recited in the present claims.

As to whether the enzymes recited in the present claims *could* be expressed using the approach described in Van Ooyen is entirely speculative. The answer to that question can only be determined after it is attempted—an experiment that is not described in the Van Ooyen reference. Thus, while one may be led to attempt to express the recited enzymes in a plant host after reading Van Ooyen, it is by no means a certain conclusion that the attempt will be successful. In short, the Van Ooyen et al. reference merely poses possibilities for research, or an invitation for further research. This list of enzymes recited in Van Ooyen does not provide "guidance" to arrive at the now-claimed invention, but merely suggest possibilities (optimistic possibilities at that). At best, the Van Ooyen reference, in combination with the secondary reference discussed below, presents nothing

more than an invitation to further experimentation. But, even if a claimed invention is "obvious to try," that does not make the claimed invention obviousness. See *In Re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988).

The *O'Farrell* court outlined when an invention is obvious, and therefore unpatentable, versus when an invention is obvious-to-try, and therefore patentable. The Court noted two instances in which a claimed invention is only obvious-to-try. First, an invention is merely obvious-to-try if it is necessary:

> to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, **where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.**" (7 USPQ2d at 1681, emphasis added, citations omitted.)

Second, an invention is only obvious-to-try where the inventors:

> explore[d] a new technology or general approach that seemed to be a promising field of experimentation, **where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it**." (*Ibid.*, emphasis added.)

Applicants submit that in the present case, both scenarios are highly relevant.

With respect to the first scenario, there are a myriad of parameters which go into the successful transformation of a plant host: the nature of the host itself (monocot, dicot, etc.), the method of transformation (particle bombardment, agrobacterium-mediated transformation, etc.), the catalytic activity of the target enzyme to be expressed and its potential deleterious effect on the host, the well-documented phenomenon of gene silencing, stage-specific or organ-specific or constitutive expression, etc. This is by no means an exhaustive list. Moreover, the prior art simply cannot provide any indication of which parameters are critical, nor can the prior art provide any direction as to which of many possible choices is likely to be successful because none of the applied references, taken alone or in any combination, disclose and enable the production of the explicitly recited enzymes in a plant host. Additionally, at least one of the applied references

includes statements evidencing the unpredictability of expressing recombinant enzymes in plant hosts. Applicants respectfully submit that the Examiner has improperly discounted these statements.

With respect to the second scenario, the applied prior art clearly only provides the most general guidance as to how to achieve the presently claimed invention. Van Ooyen admittedly does not teach the claimed invention, nor do the secondary references. The huge number of variables, and lack of any unifying predictive theory of successful transformation and expression of recombinant enzymes in plants negates the assumption that the expression of alpha-amylase and glucoamylase in a plant host, as described by Van Ooyen et al. renders obvious the transgenic production of the presently recited enzymes.

Moreover, a proper finding of obviousness requires that the predictability and/or necessity of experimentation to arrive at the claimed invention be evaluated in terms of the invention as a whole, and not as a sum of its parts. See, for instance, *Hybritech Inc v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Here, the Court held unobvious a method of using *mono*clonal antibodies of defined specificity in a prior art process which utilized *poly*clonal antibodies. The Court noted that prior art references which discussed the production of monoclonal antibodies may constitute an invitation to try monoclonal antibodies in the prior art immunoassays, but that the prior art did not render the claims obvious since they did not suggest how that end might be accomplished. In short, the Court held that:

> focusing on the obviousness of substitutions and differences instead of on the invention as a whole...[is] a legally improper way to simplify the difficult determination of obviousness. (231 USPQ at 93.)

The same rationale applies to the present application. Having described the transformation of only two enzymes in plants (enzymes which are functionally and structurally distinct from those now claimed), the teaching of Van Ooyen et al. cannot be extended to render obvious the present claims because the reference fails to provide the necessary reasonable expectation of success.

Combining Van Ooyen et al. with the secondary references to Virki et al., Henrissat et al., and/or Willmitzer et al. (alone or in any combination with the primary reference) does complete the spotty teaching of the Van Ooyen reference.

As noted earlier, Virki et al. is unrelated to the present claims. The Virki et al. reference does not describe in any fashion the production of cellulose-degrading enzymes. The Virki et al. reference does not describe the transformation of plant hosts to express any type of cellulose-degrading enzymes (or any other protein for that matter). The Virki et al. reference does not describe transforming tobacco or alfalfa to contain and express genes that encode *T. fusca* cellulase E2, *T. fusca* cellulase E3, *T. reesei* CBH I, and *A. cellulolyticus* endoglucanase E1, the enzymes explicitly recited in Claim 16.

The Virki et al. reference also does not mention transforming a plant host to express CBH I, CBH II, or EG I.

The disclosure of Virki et al. is limited to a description of the chromatographic fractionation of commercially-obtained cellulase mixtures. These commercially-available enzyme mixtures just happen to contain CBH I, CBH II, or EG I. This, however, is irrelevant to the present claims because Applicants are not claiming the enzymes themselves; Applicants are claiming an alfalfa or tobacco host transformed to express these enzymes. Example 1 of the Virki et al. reference is illustrative:

Example 1 describes the chromatic fractionation of Cytolase-123-brand enzyme (from Genencor). Cytolase-brand enzyme is produced by a genetically-engineered *microorganism*, not by a genetically-engineered *plant*.

Thus, the Virki et al. patent is irrelevant to the present claims. The reference simply does not address in any fashion the use of cellulose-degrading enzymes manufactured in recombinant plant hosts. The Virki et al. reference describes nothing more than the fractionation of conventional and commercially available cellulase mixtures into their component enzymes.

The Willmitzer reference also does not add any further relevant disclosure to that provided by Van Ooyen et al. and Virki et al. Like Van Ooyen et al., Willmitzer contains a sweeping, wholly unsupported, and non-enabling discussion of enzymes that could

possibly be expressed in plants. In terms of any disclosure that could even plausibly be considered enabling, Willmitzer provides only the most basic protocol for expressing two enzymes, totally unrelated to the now-claimed enzymes, in a transgenic plant: rennilase (an aspartic protease, EC 3.4.23.23, also known as Mucor rennin) and chymosin (another aspartic protease, EC 3.4.23.4). As noted above, the four enzymes recited in the present claims fall into totally different enzyme classifications, EC 3.2.1.4 and EC 3.2.1.91.

The Willmitzer reference is completely silent regarding the expression of any other type of enzyme. In short, combining Willmitzer with Van Ooyen et al. and Virki et al. does not yield the present invention because Willmitzer is completely silent regarding expressing any of *T. fusca* cellulase E2, *T. fusca* cellulase E3, *T. reesei* CBH I, and *A. cellulolyticus* endoglucanase E1 in an alfalfa or tobacco host. The ability to express rennilase and/or chymosin in a plant host does not render obvious the present claims because rennilase and chymosin are completely unrelated to any of the enzymes recited in Claim 16. The combined teaching of these three references thus fails to enable the production of a transformed alfalfa or tobacco plant as recited in Claim 16.

Combining Van Ooyen et al, Virki et al., and Willmitzer with Henrissat also does not teach or suggest the present invention because Henrissat, like Virki et al. is concerned with the synergy of conventional cellulose mixtures derived from microorganisms, not transformed plants. The Henrissat reference is totally silent regarding transformed plants that express any type of cellulose-degrading enzyme.

The Office's stated reason for relying on Henrissat is that it teaches the (presumably) desirable synergism of cellulose mixtures. However, this motivation is directly contradicted by the teaching of Virki et al. The entire drive of the Virki et al. work is summed up in the first paragraph of the Summary of the Invention in Virki et al:

> It has now been surprisingly found that the adverse effects of the commercial products are caused by the presence of certain enzyme combinations in the commercial grade cellulases used in said products.

The combination of these references thus presents an insurmountable problem regarding motivation to make the combination in the first place: Virki et al. teach that it is undesirable to combine cellulases, and therefore describes a means to fractionate such mixtures into their component enzymes. The Office, in direct contrast, however, cites Henrissat as being relevant to the presently claimed invention because this reference describes combining cellulases as being desirable. The two document are not reconcilable one to the other, and therefore there is not motivation to combine the two. Virki et al. teach that it is undesirable to combine cellulase; Henrissat teaches that combining cellulase is desirable. Because of their diametrically opposed conclusions, there is not motivation to combine these two documents in the first place.

In short, Henrissat adds nothing to the combined disclosure of Van Ooyen et al, Virki et al., and Willmitzer because Henrissat is completely and totally silent regarding an alfalfa or tobacco host that has been transformed to express any of *T. fusca* cellulase E2, *T. fusca* cellulase E3, *T. reesei* CBH I, and *A. cellulolyticus* endoglucanase E1.

Specifically regarding Claim 26, the Office sates that "there is a clear industrial motivation for synthesizing transgenic tobacco or alfalfa plants expressing plant polysaccharide degrading enzymes specifically for ensilage purposes" (Office Action, page 4). It is respectfully submitted that no such motivation is provided in the applied references. Claim 26 specifically recites "ensiling a plant" according to Claim 16. None of the references make any mention whatsoever of directly ensiling the transgenic plant itself as a means to improve the ensilement process. Van Ooyen is silent on the matter, as is Willmitzer. The Virki reference mentions enzymes relevant to ensiling plant matter, but wholly presumes that the enzymes are first isolated from their source. The Virki reference does not teach or suggest that the useful enzymes be produced in a plant and then the entire transgenic plant be added to the vegetable matter to be ensiled. Claim 26, however, positively requires that the transgenic plant be ensiled. Such a method of ensilement is not taught or comprehended by any of the references now of record.

Thus, it is respectfully submitted that the rejection of Claims 16-18, 21-22, and 26 under §103(a) in view of Van Ooyen et al, Virki et al., Willmitzer, and Henrissat, taken

individually or in any combination, is improper. Withdrawal of the rejection is now requested.

Rejection of Claims 19 and 20 Under 35 U.S.C. §103(a) over Van Ooyen et al. in View of Henrissat et al. and Further in View of Shiyaron et al. and Thomas et al.:

This rejection is also traversed, largely for the reasons given in the prior section.

Claim 19 and 20 explicitly require the expression of Seq. Id. No. 8 or Seq. Id. No. 9 in an alfalfa or tobacco host. For sake of argument, taking as fact that the secondary references to Thomas et al. and Shiyaron et al. disclose Seq. Id. Nos. 8 and 9, respectively, the combination of these two references with Van Ooyen et al. and Henrissat et al. still does not render obvious either of Claims 19 or 20 because the combined references fail to disclose, to a reasonable predictability of success, that the gene sequences disclosed in Thomas et al. and Shiyaron et al. can, in fact, be expressed successfully in a transgenic plant host.

As noted above, while the Van Ooyen et al. reference *mentions* a large number of enzymes, this reference adequately describes the expression in plants of only two enzymes, alpha-amylase and glucoamylase. These enzymes, as noted above, are both functionally and structurally distinct from those recited in the present claims.

The Thomas et al. patent is concerned entirely with a description of the cloning of a gene encoding the E1 endoglucanase of *A. cellulolyticus* in heterologous **microorganisms**. This reference is entirely, completely, and wholly silent regarding expressing this particular gene in a plant host.

Likewise, the Shiyaron et al. document is nothing more than a GenBank entry for *T. reesei* CBH I. Like the Thomas et al. patent, this document is wholly silent regarding expressing this particular CBH I gene in a plant host.

Combining all four of Van Ooyen et al., Henrissat et al., Shiyaron et al., and Thomas et al. does not render obvious either of Claims 19 or 20 because only one of the documents, Van Ooyen et al., makes any mention at all of expressing heterologous proteins in plants. Moreover, the Van Ooyen document adequately enables the expression of only two enzymes, enzymes that are structurally and functionally distinct from those recited in the present claims.

At best, combining Van Ooyen with the other three references, renders the invention recited in Claims 19 and 20 "obvious to try." But, as noted above, "obvious to try" is not the measure of obviousness. It remains wholly uncertain based upon Van Ooyen's description of functionally and structurally distinct enzymes, whether any other enzyme, including those described in Henrissat et al., Thomas et al., and Shiyaron et al. can be similarly expressed in a transgenic plant.

Note that, unlike the transgenic enzymes actually described in Van Ooyen, the transgenic plants recited in Claims 19 and 20 express cellulose-degrading enzymes that might very well have been highly destructive of the plant itself. Until the transformation was successfully completed by the present inventors, it could not have been predicted with any degree of certainty whether the transformation could be accomplished or not. In short, venturing a guess *a priori* whether the transformation described and claimed in the present application could be completed successfully would have been just that: a pure guess. This is because the cellulose-degrading activity of the enzymes encoded by the trangenes might very well have been fatal to the plant host. Thus, the combination of reference does not provide the required "reasonable predictability of success," minus an improper use of the Applicants' own disclosure.

For at least these reasons, Applicants respectfully submit that the rejection of Claims 19-20 under 35 U.S.C. 103(a) in view of Van Ooyen et al., Henrissat et al., Shiyaron et al. and Thomas et al. is improper. Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

Joseph T. Leone, Reg. No. 37,170
DEWITT ROSS & STEVENS S.C.
Firstar Financial Centre
8000 Excelsior Drive, Suite 401
Madison, Wisconsin 53717-1914
Telephone: (608) 831-2100
Facsimile: (608) 831-2106

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to:

Assistant Commissioner for Patents, Washington, D.C. 20231.

Date of Deposit: 9-4-01

Signature: Marcia Layton

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/373,272 Group Art Unit: 1635

Filing Date: August 12, 1999 Examiner: Epps, J.

Applicant(s): Austin-Phillips et al. Attorney Docket No.: 09820.114

Title: **TRANSGENIC PLANTS AS ALTERNATIVE SOURCE OF LIGNOCELLULOSIC-DEGRADING ENZYMES**

"CLEAN" CLAIMS AS AMENDED, 37 CFR §1.121(c)(1)(i)

16. (TWICE-AMENDED) A genetically recombinant tobacco or alfalfa plant, which is stably transformed to contain and express a gene sequence which encodes a cellulase-degrading enzyme selected from the group consisting of *T. fusca* cellulase E2, *T. fusca* cellulase E3, *T. reesei* CBH I, and *A. cellulolyticus* endoglucanase E1.

17. (AMENDED) The genetically recombinant plant of Claim 16, which is alfalfa.

18. The genetically recombinant plant of Claim 16, which is tobacco.

19. The genetically recombinant plant of Claim 16, which is alfalfa transformed to contain and express a gene sequence selected from the group consisting of SEQ. ID. NOS: 8 and 9.

20. The genetically recombinant plant of Claim 16, which is tobacco transformed to contain and express a gene sequence selected from the group consisting of SEQ. ID. NOS: 8 and 9.

21. (AMENDED) A method for producing cellulose-degrading enzymes comprising cultivating a genetically recombinant plant according to Claim 16.

22. The method of Claim 21, further comprising concentrating the cellulose-degrading enzymes.

26. (AMENDED) A method of ensilement comprising ensiling a plant according to Claim 16, whereby cellulose-degrading enzymes produced by the plant increase nutritional value of silage.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. Serial No.: 09/373,272 Group Art Unit: 1635

Filing Date: August 12, 1999 Examiner: Epps, J.

Applicant(s): Austin-Phillips et al. Attorney Docket No.: 09820.114

Title: **TRANSGENIC PLANTS AS ALTERNATIVE SOURCE OF LIGNOCELLULOSIC-DEGRADING ENZYMES**

"MARKED UP" CLAIMS AS AMENDED, 37 CFR §1.121(c)(1)(ii)

16. (TWICE-AMENDED) A genetically recombinant **[tabacco]** **tobacco** or alfalfa plant, which is stably transformed to contain and express a gene sequence which encodes a cellulase-degrading enzyme selected from the group consisting of *T. fusca* cellulase E2, *T. fusca* cellulase E3, *T. reesei* CBH I, and *A. cellulolyticus* endoglucanase E1.

17. (AMENDED) The genetically **[recombinat]** **recombinant** plant of Claim 16, which is alfalfa.

18. The genetically recombinant plant of Claim 16, which is tobacco.

19. The genetically recombinant plant of Claim 16, which is alfalfa transformed to contain and express a gene sequence selected from the group consisting of SEQ. ID. NOS: 8 and 9.

20. The genetically recombinant plant of Claim 16, which is tobacco transformed to contain and express a gene sequence selected from the group consisting of SEQ. ID. NOS: 8 and 9.

21. (AMENDED) A method for producing cellulose-degrading enzymes comprising cultivating a genetically recombinant plant according to Claim 16.

22. The method of Claim 21, further comprising concentrating the cellulose-degrading enzymes.

26. (AMENDED) A method of ensilement comprising ensiling a plant according to Claim 16, whereby cellulose-degrading enzymes produced by the plant increase nutritional value of silage.